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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/937,103 | 07/05/2002 | Sandrine Lentsch Graf | 01-1081 | 4719 |

20306 7590 01/30/2006

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| EXAMINER | |
|---|---|
| FORD, VANESSA L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

DATE MAILED: 01/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| **Advisory Action Before the Filing of an Appeal Brief** | **Application No.** 09/937,103 | **Applicant(s)** GRAF ET AL. | |
|---|---|---|---|
| | **Examiner** Vanessa L. Ford | **Art Unit** 1645 | |

***--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

THE REPLY FILED 29 November 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *NONE*.
   Claim(s) objected to: *NONE*.
   Claim(s) rejected: *2-17*.
   Claim(s) withdrawn from consideration: *NONE*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Advisory attachment.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☒ Other: Advisory attachment.

***Advisory Attachment***

1. Applicants amendment filed November 29, 2005 is acknowledged. For clarification of the record, the rejection of claims 2-8, 11-15 and 17 over LaPosta et al is a 102(e) rejection and not a 103(a) rejection as referred to in the Final Office action (mailed 8/30/2005). The Office apologizes for the typographical error.

***Rejection Maintained***

2. The rejection under 35 U.S.C. 102(e) paragraph is maintained for claims 2-8 and 11-15 and 17 for the reasons set forth on pages 3-4, paragraph 4 of the Final Office Action.

The rejection was on the grounds that LaPosta et al teach a liquid vaccine composition comprising a polysaccharide covalently bound to a protein (column 4, lines 60-65). LaPosta et al teach that sugars such as trehalose may be added to the vaccine composition to prevent aggregation (i.e. stabilize) of the vaccine composition (column 3, lines 10-26). LaPosta et al teach suitable antigens used in the vaccine include antigens from *Haemophilus influenzae, Neisseria meningitidis* and *Streptococcus pneumoniae*, Group A *Streptococcus* and Group B *Streptococcus* (column 4, lines 25-64). LaPosta et al teach that the antigens of the invention, for example, bacterial capsular polysaccharide or a fragment thereof is chemically linked to a protein carrier molecule in order to enhance immunogenicity (column 4, lines 60-64). LaPosta, et al anticipates the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's vaccine and the vaccine of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the vaccine does not possess the same material structural and functional characteristics of the claimed vaccine). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant's Arguments

A) Applicant urges that the presently claimed compositions do not encompass the compositions of LaPosta et al because LaPosta et al do not store a liquid composition comprising trehalose and antigen.

B) Applicant urges that a liquid vaccine composition will inherently undergo changes overtime and the presently claimed liquid vaccine compositions are different from LaPosta et al. Applicant urges that LaPosta et al cannot anticipate the present claims.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed June 15, 2005 have been fully considered but they are not persuasive.

A) The claims are directed to a product, a liquid vaccine composition. LaPosta et al teach a liquid composition comprising an antigen (polysaccharide bound to a protein carrier) and trehalose. It is the Examiner's position that the claim limitation "storing the liquid vaccine in the liquid state" is a process limitation in a product claim. It should be remembered that the products of the prior art reference appear to be the same as the claimed product claimed by the applicant because they appear to possess the same or similar functional characteristics. The purification or production of a

product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art. This is particularly true when properties of the product are not changed by the process in an unexpected manner. See In re Thorpe, 227 USPQ 964 (CAFC 1985); In re Marosi, 218 USPQ 289, 29222-293 (CAFC 1983); In re Brown, 173 USPQ 685 (CCPA 1972). Even if applicant's product can be shown to be of higher purity than the product of the prior art reference, applicant's needs to show some unexpected and unique utility or property, such as unexpected biologically significant increase in specific activity with which the increased purity, greater stability and/or practicality or freedom from some restrictive element or adverse side effects inherent in the product preparations of the prior art or some other secondary consideration which the additional degree of purity imparts (to which there is a basis in the specification) to applicant's product in order to overcome the aspect of the product's purity is relied upon. The prior art reference anticipates that claimed invention.

B) To address Applicant's comments regarding changes that liquid compositions undergo during storage, it should be noted that the claims do not recite any particular "changes that may be presented by the storage of a liquid composition". Therefore, Applicant is arguing limitations that are not in the claims. Applicant has provided no side-by-side comparison to show that the liquid compositions of the prior art differ from the claimed liquid vaccine compositions. Therefore, LaPosta et al anticipate the claimed invention.

3. The rejection under 35 U.S.C. 103(a) paragraph is maintained for claims 2-8, 11-15 and 17 for the reasons set forth on pages 4-6, paragraph 5 of the Final Office Action.

The rejection was on the grounds that Anderson et al teach vaccine comprising covalent attachment of capsular polymer fragment derived from bacterial capsular polymers to bacterial toxoids (column 2, lines 58-64). Anderson et al teach that suitable carrier proteins of the inventions include diphtheria and tetanus toxoids (columns 5, lines 29-36). Anderson et al teach that vaccine of the invention include vaccines against systemic infections caused by the pathogens *Haemophilus influenzae* type b, *E. coli*, pneumococcus, meningococcus, streptococcus and pseudomonas (column 6, lines 59-65). Anderson et al teach that the regulation of any reaction parameter, e.g. time, temperature, pH, etc. which affects the reactivity or rate of reaction will alter the final composition and structure of the conjugate (column 4, lines 45-49). Anderson et al teach that the vaccines of the invention have been lyophilized (column 18, lines 35-40). Anderson et al teach that the conjugates of the invention appear to convert into macromolecular aggregates after preparation (column 13, lines 67-68 and column 14, lines 1-2).

Anderson et al do not teach retaining the vaccine composition in liquid form nor does Anderson et al teach the addition of a non-reducing sugar.

However, Samaritani teaches that pharmaceutical compositions can be maintained in the liquid form to avoid processes such as lyophilization (see the Abstract). Samaritani teaches that non-reducing sugars are used to stabilized these compositions in liquid form (see the Abstract).

Samaritani does not teach the non-reducing sugar trehalose.

Sola-Penna et al teach that trehalose is more effective at stabilizing compositions than other sugars (see the Abstract and the Title). Sola-Penna et al teach that trehalose is the best stabilizer of macromolecules because trehalose has the ability to protect these molecules from thermal inactivation (see the Abstract).

It would be *prima facie* obvious at the time the invention was made to use trehalose to stabilize liquid composition comprising an antigen (polysaccharide bound to a carrier molecule) formulated in a liquid composition because Samaritani that non-reducing sugars can be used to stabilize pharmaceutical compositions that are maintained in the liquid state and Sola-Penna et al teach that trehalose is the best non-reducing sugar that can be used to stabilize of macromolecules. It would be expected barring evidence to the contrary that trehalose would be effective in stabilizing pharmaceutical compositions that are maintained in the liquid state because the prior art has shown that non-reducing sugars are effective at stabilizing pharmaceutical compositions in the liquid state.

Applicant's Arguments

A) Applicant urges that the claims are not obvious over the cited art references and the art references fail to provide information so that the skilled artisan could draw a reasonable expectation of success.

B) Applicant urges that there is no motivation in the cited art to make the claimed invention. Applicant urges that the prior must provide a suggestion or motivation to make the particular invention being claimed. Applicant urges that a general motivation is insufficient.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed June 15, 2005 have been fully considered but they are not persuasive.

A) It is the Examiner's position that the claimed invention is obvious over the cited prior art references. One of skill in the art would have a reasonable expectation of success because Samaritani et al teach that non-reducing sugars can be used to maintain pharmaceutical compositions in liquid form and Sola-Penna et al provide the motivation to use the particular non-reducing sugar trehalose in a pharmaceutical composition.

B) In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The Examiner disagrees with Applicants' assertion that the prior art references only provide a general motivation and this motivation is insufficient. It should be noted that the combination of references teach the claimed invention and particularly point out that non-reducing sugars can be used to maintain pharmaceutical compositions in liquid form without the complications that come along with lyophilization (Samaritani et al) and the prior art also point out that "trehalose" is preferred over other non-reducing sugars because trehalose is the best stabilizer of macromolecules and it has the ability to protect these molecules from thermal inactivation (Sola-Penna et al). Thus, a specific motivation to combine the prior art references is set forth within the teachings of the prior art references. Therefore, the combination of references teach the claimed invention.

4. The rejection under 35 U.S.C. 103(a) paragraph is maintained for claims 9-10 and 16 for the reasons set forth on pages 7-8, paragraph 6 of the Final Office Action.

The rejection was on the grounds that Samaritani teaches a method of preserving the immunogencity of a pharmaceutical composition maintained in liquid form over time by using non-reducing sugars to stabilize these compositions (see the Abstract and page 1).

Samaritani does not teach the non-reducing sugar trehalose.

Sola-Penna et al teach that trehalose is more effective at stabilizing compositions than other sugars (see the Abstract and the Title). Sola-Penna et al teach that trehalose is the best stabilizer of macromolecules because trehalose has the ability to protect these molecules from thermal inactivation (see the Abstract).

Samaritani nor Sola-Penna et al teach vaccine compositions comprising an antigen consisting of a polysaccharide bound to a carrier protein.

Anderson et al teach vaccine comprising covalent attachment of capsular polymer fragment derived from bacterial capsular polymers to bacterial toxoids (column 2, lines 58-64). Anderson et al teach that suitable carrier proteins of the inventions include diphtheria and tetanus toxoids (columns 5, lines 29-36). Anderson et al teach that vaccine of the invention include vaccines against systemic infections caused by the pathogens *Haemophilus influenzae* type b, *E. coli*, pneumococcus, meningococcus, streptococcus and pseudomonas (column 6, lines 59-65). Anderson et al teach that the regulation of any reaction parameter, e.g. time, temperature, pH, etc. which affects the reactivity or rate of reaction will alter the final composition and structure of the conjugate (column 4, lines 45-49). Anderson et al teach that the vaccines of the invention have been lyophilized (column 18, lines 35-40). Anderson et al teach that the conjugates of the invention appear to convert into macromolecular aggregates after preparation (column 13, lines 67-68 and column 14, lines 1-2).

It would be *prima facie* obvious at the time the invention was made to use trehalose to stabilize a liquid vaccine composition comprising an antigen (polysaccharide bound to a carrier molecule) used in a method to preserve the immunogenicity of the vaccine composition over time because Samaritani that non-reducing sugars can be used to stabilize pharmaceutical compositions that are maintained in the liquid state and Sola-Penna et al teach that trehalose is the best stabilizer of macromolecules. It would be expected barring evidence to the contrary that trehalose would be effective in stabilizing pharmaceutical compositions that are maintained in the liquid state because Samaritani teaches that non-reducing sugars can stabilized compositions in the liquid state to avoid processes such as lyophilization thereby making the compositions readily injectable.

Applicant's Arguments

A) Applicant urges that there is no motivation in the cited art to make the claimed invention. Applicant urges that the prior must provide a suggestion or motivation to make the particular invention being claimed.

B) Applicant urges that none of the cited prior art references recognize that trehalose can decrease the decay of immunogenicity of a polysaccharide-protein conjugate in a liquid vaccine.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed June 15, 2005 have been fully considered but they are not persuasive.

A) As stated above, the combination of prior art references teach the claimed invention. The prior art references also provide the motivation to add trehalose in particular, to a pharmaceutical composition that is maintained in liquid form since Samaritani et al teach that non-reducing sugars can be used to maintain pharmaceutical compositions in liquid form and Sola-Penna et al teach that trehalose is the best stabilizer of macromolecules because trehalose has the ability to protect these molecules from thermal inactivation.

Sola-Penna et al teach that trehalose is the best stabilizer of macromolecules because trehalose has the ability to protect these molecules from thermal inactivation.

B) To address Applicant's comments regarding decay of immunogenicity of a polysaccharide-protein conjugate in a liquid vaccine, it should be noted that there are no claim limitations directed to decay of immunogenicity a polysaccharide-protein conjugate in a liquid vaccine. Therefore, it is the Examiner's position that Applicant is arguing limitations that are not in the claims. There is nothing on the record to suggest that the combination of references do not teach the claimed invention.

**Status of Claims**

5. No claims are allowed.

***Conclusion***

6. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
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January 24, 2006

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